

(19)



Europäisches Patentamt  
European Patent Office  
Office européen des brevets

(11) Publication number:

**0 072 046**  
**A1**

(12)

# EUROPEAN PATENT APPLICATION

(21) Application number: 82200841.3

(51) Int. Cl.<sup>2</sup>: A 61 K 9/72, A 61 K 31/35

(22) Date of filing: 06.07.82

(30) Priority: 24.07.81 GB 8122848

(71) Applicant: Fisons plc, Fison House Princes Street,  
Ipswich Suffolk IP1 1QH (GB)(43) Date of publication of application: 16.02.83  
Bulletin 83/7(72) Inventor: Forrester, Raymond Brian, 42 Roman Way,  
Elworth Sandbach Cheshire (GB)  
Inventor: Boardman, Terence David, 92 Elmwood Road,  
Northwich Cheshire (GB)

(54) Designated Contracting States: AT DE IT NL SE

(74) Representative: Craig, Christopher Bradberry et al,  
Fisons plc 12 Derby Road, Loughborough Leicestershire  
LE11 0BB (GB)

(57) Inhalation drugs, methods for their production and pharmaceutical formulations containing them.

(57) There is described a finely divided inhalation drug, e.g. sodium cromoglycate, comprising a therapeutically effective proportion of individual particles capable of penetrating deep into the lung, characterised in that a bulk of the particles which is both unagglomerated and unmixed with a coarse carrier, is sufficiently free flowing to be filled into capsules on an automatic filling machine and to empty from an opened capsule in an inhalation device. A number of the individual drug particles have a spherical, collapsed spherical or ring doughnut shape.

There is also described a method of marking the fine particles and pharmaceutical formulations containing them.



10 μm 2000X



5 μm 5000X



5 μm 5000X



2 μm 10000X

EP 0 072 046 A1

INHALATION DRUGS, METHODS FOR THEIR PRODUCTION AND  
PHARMACEUTICAL FORMULATIONS CONTAINING THEM

This invention relates to a novel form of drug and to methods for its production and formulation.

5 In our British Patent No. 1,122,284 we have described and claimed an insufflator device for use in the administration of powdered medicaments by inhalation. With that device, and other devices, e.g. that described in British Patent Specification No. 1,331,216, and  
10 European Patent Application No. 813021839 a user inhales air through the device which causes a powder container mounted therein to rotate. Powder within the container is fluidised and dispensed into the air stream which is inhaled by the user. For optimum dispensing it has been  
15 found that the powdered medicament particles should be comparatively free-flowing and yet should have an ultimate particle size of less than about ten microns to ensure adequate penetration of the medicament into the lungs of the user. These two requirements are prima facie mutually  
20 exclusive, since such fine powders are not usually sufficiently free-flowing. It has in the past been found that this problem can be mitigated or overcome, e.g. as described in US Patent 4,161,516, by forming the powdered medicament into small soft pellets or soft granules. Both  
25 soft pellets and soft granules will fluidise satisfactorily within the container and yet are of sufficiently low internal coherence to break up into finer

particles of medicament of a therapeutically effective size in the turbulent airstream around the outside of the container. However the procedure of forming the micronised drug into soft pellets or granules is both difficult and expensive. An alternative means of getting the fine particles to flow and disperse satisfactorily has been to mix them with a coarse carrier, e.g. coarse lactose (see US Patent No. 3,957,965). However with all pharmaceuticals it is desirable to use as pure a form as possible (inter alia to avoid any possible adverse reactions by the patient to the excipients) and the presence of the coarse carrier is not therefore desirable. Furthermore the mixing of the fine drug with the coarse carrier involves the extra expense of the carrier, the possibility of segregation of carrier and drug during transport and storage, and extra process steps which add to the cost of production. Production of both the pelletised material and the blend of fine material with the coarse carrier involves the initial step of micronising the drug. Sodium cromoglycate has been made, for blending with lactose or agglomeration into soft nearly spherical pellets and administration by inhalation, as a micronised dry powder and in this form consists mostly of rods or lath-shaped crystals. In both the pelletised and blended material energy is needed to break

up the pellets or to separate the fine drug from the coarse carrier before or during inhalation. Thus in many instances it has also been found that the amount of drug which is available as fine particles in the air stream is dependent on the rate at which air is passed through the inhaler (i.e. the amount of energy imparted to the formulation). This can be particularly disadvantageous when the drug is used to treat patients suffering from conditions affecting their ability to breath.

10        Thus for many years the production of drugs in a form in which they can flow easily (and therefore be filled readily into capsules) while at the same time being of a sufficiently small particle size to penetrate deep into the lung has presented a problem which has only been  
15        capable of resolution by means of complex procedures.

         We have now found particles which can penetrate deep into the lung and yet which are sufficiently free flowing to be filled into capsules, and otherwise manipulated, without mixing with a coarse diluent or formation into  
20        soft pellets or granules. We have also found that these particles can disperse well from an inhaler at both low and high air flow rates, thus, in certain circumstances, improving consistency of capsule emptying. Furthermore we have found that the new particles can, in general, be  
25        coarser than those of the prior art while giving an

equivalent proportion of particles capable of penetrating deep into the lung.

According to the invention we provide a finely divided inhalation drug comprising a therapeutically effective  
5 proportion of individual particles capable of penetrating deep into the lung, characterised in that a bulk of the particles which is both unagglomerated and unmixed with a coarse carrier, is sufficiently free flowing to be capable of being filled into capsules on an automatic filling  
10 machine and to empty from an opened capsule in an inhalation device.

According to the invention we also provide a drug in finely divided and unagglomerated form, wherein a substantial proportion of the individual drug particles  
15 have a spherical, collapsed spherical, i.e. where one or both sides of the sphere appear to have been pushed inwards, or toroidal shape, i.e. the shape of a ring doughnut. The ring doughnut shapes may have a hole  
20 through the middle or may have a thin membrane filling the hole. In certain cases a population of two or more of spheres, partially collapsed spheres, fully collapsed spheres and ring doughnut shapes is found.

The individual particles should be as rounded and smooth as possible to enable them to be carried easily in  
25 an air stream and to flow readily on capsule filling

machines. We prefer the majority of the particles not to have sharp or broken edges, and for the particles themselves to be mechanically strong so that they do not break during encapsulation or on their passage from the capsule to the lung. Thus we prefer to avoid hollow shell particles. We particularly prefer a proportion of the particles, especially when the drug is sodium cromoglycate, to be toroidal in shape. In general the shape of the particles is unrelated to particle size. We have also found that in general the particles have smooth cleavage planes, are relatively non-porous and are of uniform density through each particle. With respect to their strength the particles of the present invention are strongly differentiated from the prior art soft pellets and granules, and with respect to their shape they are strongly differentiated from the prior art micronised material. A low particle density in the material is indicative of fragile particles and is, in general, to be avoided. We prefer the particles to be as uniform as possible in all respects.

The surface texture of the particles will vary according to the particular drug concerned and the techniques used to produce the particles, and can vary from a highly convoluted (brain like) structure to a random fluffy or to a smooth texture. In general we

prefer to avoid highly convoluted surface textures.

The roughness of the surface of the particles can be determined by measuring the total surface area of the particle by the Brunauer, Emmett and Teller (BET) method (British Standard 4359 (1969) Part 1) and comparing this with the envelope surface area of the particles as measured by permeametry (Papadakis M. (1963), Rev. Mater. Construct. Trav. 570, 79-81).

We prefer the permeametry: BET ratio to be in the range 0.5 to 1.0, preferably 0.6 to 1.0 and more preferably 0.7 to 0.97 (note a ratio of 1.0 represents a perfectly smooth particle). By way of contrast prior art micronised drugs, e.g. micronised sodium cromoglycate, have a permeametry: BET ratio of about 0.32.

We prefer the particles of the invention to be as strong and as dense as possible. The particle density of the particles (as opposed to the bulk density) may be measured by

a) the petroleum ether method in which a known weight (25g) of powder is weighed into a measuring cylinder, a known amount of petroleum ether (50ml) is added and the mixture shaken until all the powder is suspended. The inner walls of the measuring cylinder are washed with a small amount of petroleum ether (10ml). Knowing the weight of powder used, the volume of petroleum ether added

0072046

and the final suspension volume, the particle density can be calculated.

or b) the air pycnometer method in which a given amount of powder is placed in a chamber which is hermetically sealed. The volume of the chamber is gradually reduced by a moving piston until a specified pressure is reached. The position of the piston indicates the volume of the powder particles, hence the particle density can be calculated.

We prefer the particles, e.g. of sodium cromoglycate, to have a particle density according to the above methods of from about 1.3 to 1.7 and preferably from 1.3 to 1.6 g/cm<sup>3</sup>.

The micronised material, e.g. sodium cromoglycate, of the prior art has a loose bulk density of about 0.21 g/cm<sup>3</sup> and a packed bulk density of about 0.29 g/cm<sup>3</sup>. In measuring loose bulk density a suitable amount of powder (40g) is poured, at an angle of 45°, into a measuring cylinder (250ml). The volume occupied by the powder in the measuring cylinder when related to the original mass of powder provides the measure of "loose bulk density". If the powder, in the cylinder, is tapped or jolted, e.g. using the Engelsmann Jolting Volumeter, until a stable volume is attained (500 jolts) then the lower volume after jolting when compared with the original



mass of powder provides the measure of "packed bulk density".

It is also known, e.g. from British Patent Specification No. 1,549,229 that hard granules of sodium cromoglycate of particle size 60 to 200 microns (measured by sieving) can have higher bulk densities than the micronised material. However these hard granules were not designed for, and indeed would be unsuitable for, inhalation. Surprisingly we have found that the particles of the present invention have a higher bulk density than micronised material, e.g. micronised sodium cromoglycate. We prefer the particles of the present invention to have a loose bulk density of greater than about  $0.3 \text{ g/cm}^3$ , preferably of greater than  $0.35 \text{ g/cm}^3$ , more preferably of from  $0.35$  to  $0.5 \text{ g/cm}^3$ , and most preferably  $0.35$  to  $0.4 \text{ g/cm}^3$ ; and a packed bulk density of from about  $0.4$  to  $0.75 \text{ g/cm}^3$  and preferably of from  $0.55$  to  $0.6 \text{ g/cm}^3$ . The bulk densities of materials are, in general, relatively independent of the particular material used, but are dependent on the shape, size and size distribution of the particles involved.

We prefer the particles of the invention, when they comprise sodium cromoglycate and are intended for administration as a dry powder in, for example, a gelatine capsule to have a moisture content of from 5 to 14, and

preferably from 8 to 11% w/w. Before filling into the capsule the powder will tend to be at the lower end of the moisture range, and after filling to be at the upper end of the range. Sodium cromoglycate powders according to the invention may also be made containing very low, e.g. less than 1%, or preferably less than 0.5%, w/w, quantities of water. These very dry powders may be used in pressurised aerosol formulations. The water contents in this specification are those measured by drying a small sample (1 to 2g) for 15 hours at 105°C in a vacuum oven (less than 5mm Hg) in the presence of phosphorus pentoxide.

Examples of suitable medicaments include those used for the inhalation treatment of allergic airway diseases such as pharmaceutically acceptable salts of 1,3-bis(2-carboxychromon-5-yloxy)propan-2-ol; bronchodilators, e.g. isoprenaline, salbutamol, fenoterol, terbutaline, reproterol etc and salts of any one thereof; antibiotics, e.g. tetracycline; steroids, e.g. beclomethasone dipropionate; enzymes; vitamins and antihistamines. If desired a mixture of medicaments, for example a mixture of sodium cromoglycate and a bronchodilator, such as isoprenaline, terbutaline, fenoterol, reproterol or a salt of any one thereof, may be used. Where a highly active medicament is used which requires a small unit dose the individual particles may

comprise the active ingredient together with a suitable diluent, e.g. lactose. The incorporation of the diluent in the particle avoids the possibility of segregation which is possible when individual fine particles of active ingredient are used with separate coarse particles of diluent.

We prefer that at least 50% by weight and preferably more than 90%, of the drug particles are of less than 60 microns, more preferably of less than 40 microns, most preferably of less than 20 microns and especially of less than 10 microns, e.g. less than 8 microns in diameter. We particularly prefer at least 50% of the particles to be of 2 to 6 microns in diameter. In general the smaller the mass mean diameter of the material the higher will be the dispersion of the material, as measured by the test of Example A(a).

Material according to the invention, e.g. sodium cromoglycate, having a median diameter of from 10 to 15 microns can, because of the enhanced aerodynamic properties of the particles, be equivalent in emptying and dispersion properties (see Example A) to micronised (i.e. sub 10 micron) material which has been formed into soft pellets as described in US Patent 4,161, 516 or blended with coarse lactose as described in US Patent 3,957,965.

The particle sizes in this specification are those

measured with a Coulter Counter TALL used in a standard laboratory environment, or the pipette centrifuge. In measuring particle sizes with a Coulter Counter, the sample to be analysed is dispersed in an electrolyte into which dips a glass tube. The glass tube has a 50 to 400 micron hole through the wall thereof with electrodes mounted on either side of the hole in the tube wall. The tube is immersed sufficiently for the hole and electrodes to be submerged in the liquid. The suspension is made to flow through the hole in the glass tube and as each particle passes through the orifice it displaces its own volume of electrolyte, thus changing the resistance across the hole. This change in resistance is converted into a voltage pulse with an amplitude proportional to the particle volume. The pulses are fed to an electronic counter with an adjustable threshold level such that all pulses above the threshold are counted. By setting the threshold level at different values it is possible to determine the number of particles falling within given size ranges and thus the proportion of particles in a sample which fall outside a desired particle size range. The Coulter Counter measures the volume of a sphere having the same volume as the unknown material, i.e. it measures a volume diameter.

In measuring particles by the pipette centrifuge

(Christison Scientific Equipment Limited) the powder is suspended in a suitable liquid (e.g. n-butanol). The suspended sample is put in a constant speed centrifuge. Samples are withdrawn from the centrifuge at selected time intervals. The level of solids in each sample is measured (normally by drying) and the average diameter calculated using an equation derived from Stokes Law (Particle Size Measurement Published by Chapman Hall 3rd Ed. Dr. T. Allen, page 377 et seq.). The pipette centrifuge measures a mass, or Stokes, diameter.

The Coulter counter (with a 100 micron hole) is able to measure particle sizes of from about 2 to 40 microns and the pipette centrifuge is able to measure particle sizes down to about 0.2 microns.

According to the invention we also provide a process for the production of finely divided drug, which comprises atomising and drying a solution of the drug and collecting some or all of the particles which are below 60, preferably below 40, more preferably below 20 and especially below 10 microns in diameter. The particles are preferably of the sizes given above.

Spray or flash drying of materials is well established as a drying technique in the food and other industries, but is scarcely used at all in the pharmaceutical industry. Thus spray drying is routinely used in the

production of coarse particle products such as dried milk, instant coffee and dextran. The use of spray drying techniques to produce very fine powders is not conventional and is unknown in the pharmaceutical field, the normal technique for producing such fine powders being to make, and then micronise, a crystalline drug. The use of a spray drying technique is advantageous in that it is adapted to suit large batch productions, thus decreasing the amount of quality control required and also in that it may remove the need for recrystallisations and micronisation to get the drug into the desired form.

Any suitable form of atomiser can be used. Atomisation results from an energy source acting on liquid bulk.

Resultant forces build up to a point where liquid break-up and disintegration occurs and individual spray droplets are created. The different atomisation techniques available concern the different energy forms applied to the liquid bulk. Common to all atomisers is the use of energy to break-up liquid bulk. Centrifugal, pressure and kinetic energy are used in common forms of atomiser.

Sonic and vibratory atomisers are also used. Specific atomisers which may be mentioned include rotary atomisers, e.g. those involving vaned wheels, vaneless discs, cups, bowls and plates; pressure atomisers, e.g. those involving pressure nozzles, centrifugal pressure nozzles, swirl

chambers and grooved cores; kinetic energy or pneumatic atomisers, e.g. those involving two or three fluids, or internal or external mixing; and sonic energy nozzles, e.g. involving sirens or whistles. We prefer to use kinetic or pneumatic energy atomisers particularly two fluid pressure or syphon or sonic nozzle atomisers. In general two fluid pressure nozzles tend to produce powders having more desirable characteristics than two fluid syphon nozzles and two fluid pressure nozzles also tend to give more reproducible results and use less energy.

The atomiser can be used in a spray or flash drying apparatus.

The conditions of operation of the apparatus and storage of the solution (e.g. pH and temperature) should clearly not be such as to degrade the drug, or introduce impurities, or biological contamination, into the drug.

The spray drying apparatus preferably comprises the atomiser, a main chamber, one or more (e.g. two) cyclones, a bag filter and, if desired or necessary to maximise recovery, a terminal wet scrubber or electrostatic precipitator. The particle collection system is designed to capture the desired size range of particles and also to maximise the yield. All over and under size material may be recovered and recycled or put to other uses.

The solution of the drug may be in any suitable

-16-



suitable.

The temperature of the solution to be fed to the spray drier will vary with the drug and the solvent to be used. In general we prefer to use a temperature at which the solution can be stored for a long period in large batches without degradation. As high a temperature as possible comensurate with stability is desirable to reduce solution viscosity and provide energy to the drying process.

The air flow rate, direction into the spray drier, the temperature of the air and the rate of feed of solution to the spray drier can be optimised by simple experiment. All of the parameters in the spray drying process interrelate and can be adjusted to produce the desired product.

Gases other than air, e.g. nitrogen, can be used if desired. The use of an inert gas will be advantageous when an inflamable solvent or a readily oxidisable drug is used. The gas used, e.g. air or nitrogen, may, if desired, be recycled to avoid loss of entrained drug and/or to conserve energy and the inert gas.

The particle size of the product will be set by the concentration of the feed solution, the rate of feed to the spray drier, the means of atomising the solution, e.g. the type of atomiser and the pressure of the air, and solution to be dried, the temperature and temperature

gradient within the drier and, to a small extent, the air flow in the drier. The particle size and air flow will then dictate where the desired product is collected and the means of collection.

5 The particle size of the product tends to remain fairly constant with liquid flow rate through the atomiser, but to decrease with increasing air pressure up to a limiting pressure, e.g. of about  $11\text{Kg cm}^{-2}$ . The range of air pressures suitable will naturally depend on  
10 the atomisation device used, but we have found that air pressures of from about  $2\text{Kg cm}^{-2}$  to  $11\text{KG cm}^{-2}$  are in general effective, e.g. with a 0.4mm orifice syphon two fluid nozzle. In order to achieve reproducible results we prefer to maintain a constant air flow to the dryer and  
15 appropriate air flow control devices may be used if desired.

The cyclone or cyclones used to collect the dried particles are of conventional design, but adapted to  
20 collect finer particles than is normal. Thus the pressure differential across the cyclones, the combination of two or more cyclones and the design of the particular cyclones used may be adjusted to enable capture of the fine particles. The bag filter used to collect the finest material is of conventional design and is readily  
25 available. The filter medium within the bag filter

preferably has a high capture efficiency for particles of approximately 0.5 microns in diameter and greater. A particularly suitable medium is a polytetrafluoroethylene membrane supported on a polypropylene or polyester cloth, e.g. a needle felt cloth. Any electrostatic precipitator, or wet scrubber, used will also be of conventional design.

The product may be classified, e.g. sieved or air classified, to remove over and under sized material. The over and under sized material may be recycled or used for other purposes.

The final product may be put up in any suitable form of container such as a capsule or cartridge. Where it is desired to use the product in association with other ingredients such as colourants, sweeteners or carriers such as lactose, these other ingredients may be admixed with the particles of the invention using conventional techniques or may be incorporated in the solution to be spray dried. We prefer the particles of the invention to contain medicament and water only. Mixtures of two or more different particles according to the invention, e.g. of sodium cromoglycate and a bronchodilator, such as isoprenaline sulphate or terbutaline sulphate, may be made and filled into suitable containers.

According to our invention we also provide a method of application of a medicament, e.g. sodium cromoglycate, to

a patient by way of inhalation, the medicament being dispersed into an air stream, characterised in that an opened, e.g. pierced, container, e.g. capsule, containing particles according to the invention is rotated and vibrated in an air stream which is inhaled by the patient. The rotation and vibration may conveniently be produced by any one of a number of devices, e.g. the device of British Patent Specification No. 1,122,284.

The particles according to the invention may also be used in pressurised aerosol formulations (together with propellant gases, e.g. a mixture of two or more of propellants 11, 12 and 114, preferably with a surface active agent, e.g. sorbitan trioleate) or may be formed into soft pellets, e.g. as described in US Patent Specification No. 4,161,516, or may be used for application to the skin. Sodium cromoglycate is known to be of use in the treatment of a wide variety of conditions, e.g. asthma and hay fever.

From another aspect the invention also provides a capsule, cartridge or like container containing particles according to the invention, optionally in association with other particles. We prefer the container to be loosely filled to less than about 80% by volume, preferably less than about 50% by volume, with the particles of the invention. The particles are preferably not compacted.

into the container. We prefer the container, e.g. capsule, to contain from 10 to 100 mg, e.g. about 20mg, of the particles.

The invention will now be illustrated by the following Examples in which all parts and percentages are by weight unless otherwise stated..

Example 1

The active compound (A) was dissolved in a solvent, normally water, to a concentration B (% w/v). This solution flowed under pressure or vacuum to the atomiser. At the atomiser the solution temperature was normally greater than 50°C. Conditions of atomisation (C) and of droplet drying (D) were preset and remained constant throughout the run. The powder was captured in the drying chamber, in two cyclones (firstly a Vantongerren Buell AC 130 cyclone of diameter 22 cm and height 74 cm and secondly a high efficiency Stairmand formula cyclone of diameter 14 cm) and finally in a bag filter which had as the filter media polytetrafluoroethylene lined polypropylene. At the end of each run the contents of each collection vessel was weighed (E) and sized (F) (Coulter Counter Model TALL).

a) Varying Active Ingredients

Using a concentration (B) of 10% w/v in water, and atomisation conditions (C) a pressure two fluid nozzle

(0.4mm orifice), a solution flow rate of  $65 \text{ ml min}^{-1}$  and an atomisation pressure of  $27 \times 10^3 \text{ Kg m}^{-2}$  the results shown in Table 1 were obtained.

Note - Electron micrographs (see Figures 1 to 4) showed.

Salbutamol Sulphate - smooth spheres

Terbutaline Sulphate - "orange peel" spheres

Isoprenaline Sulphate - smooth spheres

4,6-Dioxo-10-propyl-4H,6H-pyrano[3,2-g]

pyran-2,8-dicarboxylic acid disodium salt "orange peel" spheres with surface cracks

Sodium Cromoglycate )

Sodium Cromoglycate/ ) "doughnut", spheres and other active ingredients) collapsed spheres

#### 15 b) Varying Atomisation Techniques

Active ingredient (A) - Sodium Cromoglycate.

Conditions used and results obtained are given in

Tables 2 and 2a.

Two fluid syphon nozzle - CT (London) Ltd. CT Type  
J1A 16/50 (4mm orifice)

Two fluid pressure nozzle - CT (London) Ltd. CT Type  
J11

Ultrasonic nozzle - Ultrasonics Ltd, Q35 H  
Sonicore nozzle

Swirl Air nozzle - Delevan Ltd - Swirl Air

Nozzle Type 32163-1

c) Variation of Powder Collection Techniques

The powder is collected in the drying chamber, cyclones and a bag filter.

5 Active ingredient A - Sodium Cromoglycate.

Conditions used and results obtained are given in Tables 3 and 3a.

Powder Capture Equipment

10 Main chamber (MC) size - 13 cu ft (give metric equivalent)

Cyclone A - Stairmand High Efficiency  
Cyclone (Diameter 14cm)

Cyclone B - Vantogeren Buell AC 130  
Cyclone (Diameter 22cm,  
15 Height 74cm)

Cyclone C - Stairmand High Efficiency  
Cyclone (Diameter 11.9cm)

Bag Filter (BF) - 1.86 M<sup>2</sup> polytetrafluoro  
ethylene lined polyester

20 d) Variation of Droplet Drying Time

Droplet drying time is dependent upon both the temperatures used in drying, i.e. air inlet temperature, the residence time in the drying chamber (normally this is as a result of drying chamber size) and level of  
25 evaporation required. Residence time can be changed by

- modifying the drying air flow rate but this results in a significant change in efficiency of capture within the latter cyclones. Table 4 indicates the range of drying conditions used. Increased residence time (i.e. slower drying) produces improved particles with improved performance.

Electron micrographs of a selection of the above powders are shown in the accompanying Figures. Figures 11 and 12 are electron micrographs of, respectively pelletised sodium cromoglycate, and micronised sodium cromoglycate and are included for comparison purposes only. In each of Figures 1 to 12 the magnification and an approximate scale is given.

15

20

25



TABLE 1

RUN NO.	ACTIVE INGREDIENT (A)	DRYING CONDITIONS (D)				POWDER RECOVERED E/F				ELECTRON MICROGRAPH
		INLET TEMP.	OUTLET TEMP.	AIR FLOW RATE	MAIN CHAMBER	CYCLONE B	CYCLONE A	CYCLONE volume median diameter		
		°C	°C	m <sup>3</sup> s <sup>-1</sup>						
1.	Sodium Cromoglycate	195	100	0.034	2.0/-	80/7.5	18/3.4	1 (B cyclone)		
2.	Terbutalene Sulphate	202	102	"	-/-	83/4.3	17/4.0			
3.	Salbutamol Sulphate	204	105	"	-/-	78/4.1	22/2.7			
4.	Isoprenaline Sulphate	201	100	"	33/-	34/6.5	33/3.3			
5.	4,6-Dioxo-10-propyl-4H,6H-pyranol[3,2-g]pyran-2,8-dicarboxylic acid disodium salt	200	100	"	7/16.5	78/6.2	15/4.1		2 (B cyclone)	
6.	Sodium Cromoglycate (100)/									
7.	Terbutalene Sulphate (0.522) w/w	200	101	"	8/-	75/6.6	17/3.6	3		
	Sodium Cromoglycate (100)/									
	Salbutamol Sulphate (0.522) w/w	220	88	"	17/-	58/7.4	25/4.2			
8.	Sodium Cromoglycate (100)/								4	
	Isoprenaline Sulphate (0.522) w/w	205	106	"	13/19.0	75/7.0	12/3.2			
9.	Salbutamol Sulphate * (1.6)/							93/7.8 (cyclone C)		
	Lactose (100) w/w	200	100	"	7/-					

\* Cyclone configuration changed to MC/C/BF.

3126/8495E/109/sm

0072046

TABLE 2

ATOMISATION CONDITIONS (C)				DRYING CONDITIONS (D)			POWDER RECOVERED E/F						
RUN	ATOMISER	SOLUTION		ATOMISATION		INLET		OUTLET		AIR FLOW RATE	MAIN CYCLONE	CYCLONE BAG	ELECTRON FILTER MICROGRAPH
		CONC	FEED RATE	PRESSURE	TEMP.	TEMP.	CHAMBER B	A					
NO.	TYPE	% w/v	ls <sup>-1</sup> x10 <sup>-3</sup>	Kgm <sup>-2</sup> x10 <sup>3</sup>	°C	°C	m <sup>3</sup> s <sup>-1</sup>	micron volume median diameter					Figure No
10.	SLOTTED DISC	10	0.57	23000	220	134	0.034 *	91/15	9/5.2				5 (B cyclone)
11.	SLOTTED DISC	10	0.48	rpm	214	130	"	20/-	78/22	2/4.0			
12.	HOLED DISC	10	0.70		220	118	"	32/-	65/17	3/4.3			
13.	INVERTED CUP	10	0.50		215	127	"	21/24	79/17.7				6 (B cyclone)
14.	TWO FLUID SYPHON	5	0.33	150.7	238	125	0.034 1/-	19/4.5	31/2.8	49/-			
15.	NOZZLE	20	1.33	150.7	205	94	"	26/15.5	12/7.4	62/3.1			
16.		10	0.90	56.4	210	108	"	7/-	70/8.5	23/3.0			
17.		10	0.63	105.7	225	113	"	5/-	34/4.7	31/2.9	30/2.1		
18.	TWO FLUID	15	0.37	28.2	190	132	0.034 8/29	62/6.8	30/3.7				
19.	PRESSURE	10	0.33	28.2	200	95	"	12/-	77/9.2	11/3.5			
20.	NOZZLE	10	1.52	18.3	210	104	"	24/-	74/16.0	2/4.0			
21.	4mm orifice	10	0.42	39.5	203	137	"	5/25	53/10	33/3.4	9.3/0 7 (A cyclone)		
22.	TWO FLUID	10	1.33	36.6	205	95	0.034 13/-	77/10.5	10/3.2				
23.	PRESSURE NOZZLE 5mm orifice	10	1.17	21.1	205	90	"	12/-	79/9.2	9/4.2			
24.	ULTRASONIC NOZZLE	10	1.47	35.2	210	87	0.034 6/-	82/9.6	12/3.3				8
25.	SWIRL AIR NOZZLE	15	1.17	49.3	200	90	0.034 13/-	79/14.5			8/-		9
* Chamber contents showed incomplete drying.													

\* Chamber contents showed incomplete drying.

3126/8496A/109/5M

0072046

TABLE 2a

Run No.	Dispersion (see Exam-ple Aa)	Coulter Particle size	Density g/cm <sup>3</sup>	Bulk Density g/cm <sup>3</sup>	Moisture (see Exam-ple Ab)	Emptying	BET Permeametry	Permeametry BET ratio
Air Pyon- Petro- Loose Packed								
			ometer	leum	Ether			
% w/w	volume median diameter		% w/w	%	m <sup>2</sup> g <sup>-1</sup> x10 <sup>3</sup>			
10. 12.6	15	-	-	86	-	-	-	-
10. 41.4	5.2	-	-	80	-	-	-	-
11. -	22	1.35	1.45	-	0.612	0.496	-	0.79
12. -	17	-	-	88	-	-	-	-
12. 40.0	4.3	-	-	55	-	-	-	-
13. -	17.7	1.56	-	88	0.43	0.33	-	0.69
14. -	2.9	-	-	57	-	-	-	-
15. 8.6	15.5	-	-	93	-	-	-	-
17. 21.4	2.8	1.59	1.66	59.2	2.42	1.25	-	0.52
20. -	24	1.33	1.45	98	-	-	-	-
23. 19.6	9.2	-	-	92	-	-	-	-
23. 26.1	4.2	-	-	28	1.75	1.1	-	0.63
24. 12.3	14.5	1.56	1.55	96.3	-	-	-	-
25. 24.4	9.5	-	-	96	-	-	-	-

0072046

TABLE 3

RUN NO.	POWDER CAPTURE EQUIPMENT CONFIGURATION	ATOMISATION CONDITIONS (C)				DRYING CONDITIONS (D)				POWDER RECOVERED (E/F)			
		SOLUTION		ATOMI-	INLET	AIR FLOW		MAIN	CYCLONE		CYCLONE	BAG	
		CONC	FEED RATE	TYPE	TEMP.	RATE	CHAMBER	A	B	C	FILTER		
		% w/v	ls <sup>-1</sup> x10 <sup>-3</sup>	Kgm <sup>-2</sup> x10 <sup>3</sup>	°C	°C	m <sup>3</sup> s <sup>-1</sup>	volume median diameter microns					
26.	MC/A/B/BF	TWO FLUID SYPHON NOZZLE	10	1.17	105.7	210	95	0.034	3/-	87/9.6	10/4.2		
27.	MC/BF	"	10	1.27	105.7	215	98	0.034	14/17			86/5.2	
28.	MC/B/A/BF	"	10	0.88	105.7	218	112	0.034	3/-	40/2.9	35/5.4	22/2.0	
29.	MC/BF	TWO FLUID PRESSURE NOZZLE 4mm	10	1.5	18.3	180	80	0.034	50/-			50/13.5	
30.	MC/BF	NOZZLE 4mm	10	0.42	33.8	190	120	0.034	4/23			96/5.2	
31.	MC/B/A/BF	ORIFICE	10	1.52	18.3	210	104	0.034	24/-	3/4.0	73/16		
32.	MC/C/BF		10	0.9	35.2	195	95	0.034	11/-			86/6.5	3/-
33.	MC/BF	TWO FLUID PRESSURE NOZZLE 5mm	10	1.73	16.2	185	74	0.034	61/-			39/14	
34.	MC/B/A/BF	NOZZLE 5mm	10	1.16	21.1	205	90	0.034	12/-	9/4.2	79/9.2		
35.	MC/C/BF	ORIFICE	15	1.23	26.8	222	102	0.034	16/-			86/11.5	

0072046

TABLE 3a

Run Dispersion No. (see Example Ac)	Pipette Centrifuge particle size	Coulter Particle Density $g/cm^3$	Bulk Density $g/cm^3$	Moisture (see Example Ab)	Emptying BET	Permeametry BET	Permeametry BET ratio
Air Pycn- Petro- Loose Packed							
ometer leum Ether							
% w/w	mass median diameter	volume median diameter		% w/w	%	$m^2 kg^{-1} \times 10^3$	
26. 25.4	-	4.2	-	-	91	-	-
27. 8.3	-	17.0	-	-	95	-	-
28. -	1.7	2.0	-	-	95	-	-
29. 17.1	-	13.5	-	-	97	-	-
31. -	-	24.0	1.45	-	98	-	-
32. 20.6	-	8.5	-	-	93	-	-
33. 20.0	-	14.0	-	-	97	-	-
34. 19.6	-	9.2	-	-	92	-	-
26.1	-	4.2	1.56	0.43	98	1.75	1.12
35. 20.9	-	11.5	-	8.1	92.9	-	0.64

0072046

- 30 -

TABLE 4

ATOMISATION CONDITIONS					DRYING CONDITIONS			
RUN NO.	ATOMISER TYPE	SOLUTION CONC.	SOLUTION FEED RATE	ATOMISATION PRESSURE	INLET TEMP.	OUTLET TEMP.	AIR FLOW RATE	ELECTRON MICROGRAPH FIGURE
		% w/v	Ls <sup>-1</sup> x10 <sup>-3</sup>	Kgm <sup>-2</sup> x10 <sup>3</sup>	°C	°C	m <sup>3</sup> s <sup>-1</sup>	
36.	Two Fluid	20	1.67	176.2	165	88	0.034	
37.	Syphon Nozzle	5	0.48	55.0	345	254	0.034	
38.	Two Fluid Pressure Nozzle 4mm	10	0.67	35.2	305	122	0.034	10 (1st cyclone)
39.	Orifice	10	1.28	23.3	140	60	0.034	

0072046

0072046

Example 2

The experiment was carried out using a spray drier which had a main chamber and a single cyclone. (Main chamber 0.37m<sup>3</sup>, cyclone Stairmand High Efficiency design with diameter 119mm). Atomisation was achieved using a two fluid pressure nozzle with orifice diameter 0.44mm. With an aqueous sodium cromoglycate feed solution concentration of 15 % w/v, an air flow rate of 0.034M<sup>3</sup>s<sup>-1</sup> and other conditions set out in Table 5, the results shown in Tables 5, 5a and 5b were obtained. Table 5b gives test results when the powders produced according to this Example have been filled into hard gelatine capsules.

TABLE 5

ATOMISATION CONDITIONS (C)			DRYING CONDITIONS (D)		POWDER RECOVERED E/F	
RUN NO.	SOLUTION FEED RATE $LS^{-1} \times 10^{-3}$	ATOMISATION PRESSURE $Kgm^{-2} \times 10^3$	INLET TEMP $^{\circ}C$	OUTLET TEMP $^{\circ}C$	MAIN CHAMBER $\% / \text{Micron Volume Median Diameter}$	CYCLONE
40.	1.33	27.5	190-200	70-80	33/-	67/13.0
41.	1.58	21.1	220-230	85-95	40/-	60/14.7
42.	1.43	25.4	195-200	80-90	20/-	80/13.8
43.	1.50	24.0	195-204	75-85	33/-	67/13.7
44.	1.58	22.6	190-200	70-80	36/-	64/14.0
45.	1.50	24.0	195-205	80-90	34/-	66/16.5

0072046



0072046

TABLE 5b

CAPSULE DATA

-34-

TEST	RUN NUMBER			
	40	41	42	43
<u>Moisture Content % w/w</u>				45
Powder when in the capsule	12.1	11.9	12.2	13.3
Capsule shell	13.9	14.2	13.3	13.5
Total mg/capsule	11.8	11.9	11.9	11.6
<u>Emptying Test % w/w</u> <u>(See Example Ab)</u>				
Mean	95.4	96.4	97.1	97.2
Range	87.3-99.1	92.6-99.3	93.1-100	95.5-98.9
Dispersion mg/capsule (See Example Ac)	5.32	4.03	4.74	4.97
				4.28
				3.12

0072046

Example 3Pressure Nozzle

The trial was carried out using a spray drier having a main chamber and a single cyclone.

5 This experiment was used to demonstrate that the pressure nozzle was capable of providing small particles and establishing the order of magnitude of pressure required to produce particles with an average mass mean diameter of less than 10 microns. An atomiser pressure of 10  $2.1 \times 10^6 \text{ Kgm}^{-2}$ , a feed concentration of 6% w/v of aqueous sodium cromoglycate, an air inlet temperature of  $230^\circ\text{C}$  and an air outlet temperature of  $120^\circ\text{C}$  was used. The resulting powder had particles of size 11 microns mass mean diameter with a particle bulk density 15 similar to that of micronised powder, but with a tapped bulk density twice that of micronised powder. The powder was satisfactory in the capsule emptying test.

The appearance of the powder under the light microscope was of uniform spheres or collapsed spheres 20 with negligible fractured particles.

Example A

The drug is dispensed from a gelatine capsule 6.4mm in diameter and having two holes 0.8mm in diameter in a shoulder thereof mounted in a device (commercially 25 available under the Registered Trade Mark 'Spinhaler')

0072046

according to British Patent No. 1,122,284 having a drawn wire shaft 2.03mm diameter journalled in a hard nylon bearing tube 13mm long and having an internal diameter of 2.08mm at its inner end (i.e. that end housing the free end of the shaft) and of 2.44mm at its other end.

The particles are preferably such that when put up in gelatine capsules 6.4mm in diameter each containing 20mg of the particles they meet the criteria set out in the tests below:-

(a) Dispersion test

The filled capsules are mounted in the capsule holder of the powder insufflator (having the specific dimensions set out immediately above) of British Patent Specification No. 1,122,284 and pierced to produce two holes of 0.8mm diameter in a shoulder of the capsule. The dispersion of the medicament in the cloud delivered by the insufflator is determined using a modified version of the multistage liquid impinger described in British Patent Specification No. 1,081,881. The modifications incorporated in the present design are the addition of an extra impingement stage, and of a glass tube with a right angled bend approximately mid-way along its length. The extra impingement stage was added prior to the three stages described in British Patent Specification No. 1,081,881 and consists essentially of a jet of internal diameter

2.5cm and a collection plate of diameter 5cm designed to give an effective cut-off of approximately 12 microns at an air flow rate of 60 litres per minute! The glass tube, also of internal diameter 2.5cm abutts the external end of the jet of the extra stage. The insufflator is inserted into the upper, horizontal end of the glass tube and air drawn through at 60 litres per minute for 30 seconds. At least five capsules are treated in this manner and the results are averaged. The weight of the medicament collected on each stage of the impinger, on the glass tube, and on a filter paper positioned after the final stage is determined spectrophotometrically after solution in an appropriate volume of distilled water (or by any other appropriate method).

The particles disperse satisfactorily if an average total for each capsule of at least 0.5mg, preferably at least 2.5mg and most preferably at least 5.0mg of the particles are found on a combination of the last two stages and filter paper of the multi-stage liquid impinger.

(b) Emptying test

The filled capsules are mounted in the capsule holder of the powder insufflator (having the specific dimensions set out above) of British Patent Specification No. 1,122,284 and pierced to produce two holes of 0.8mm diameter in a shoulder of the capsule. The insufflator is

placed in a device adapted to suck air through it for 2.5 seconds, the air flow rate at no time exceeding 60 litres per minute, and being held at 60 litres per minute for at least 2 seconds. The capsule mounted in the insufflator is subjected to 4 sucks as described and the weight of the material remaining in the capsule is determined. The above procedure is repeated 20 times and the average of the results determined.

The capsules empty satisfactorily if an average of at least 50%, preferably at least 75% and most preferably at least 90% by weight of the material has emptied from each capsule.

(c) Dispersion

Single Stage Impinger

In a further refinement, the multistage liquid impinger of Example Aa) was simplified to give a single stage liquid impinger, consisting of a single impingement assembly with a filter downstream. The impingement assembly consisted of a vertical jet of internal diameter 1.9cm and a collection plate of diameter 3.8cm. At the upper end, the jet was bent through an angle of 90° and the insufflator was attached to the distal end of this horizontal portion. The impingement characteristics of this single stage device were intended to be such that material reaching the filter of this device is similar in

particle size to that reaching the final two stages and filter of the multistage liquid impinger of Example Aa). The percentage of material reaching the filter of the device is determined.

- 5 In all samples of sodium cromoglycate prepared by the techniques exemplified above at least some of the particles were of toroidal (ring doughnut) shape.

10

15

20

25

What we claim is:-

1. A finely divided inhalation drug comprising a therapeutically effective proportion of individual particles capable of penetrating deep into the lung, characterised in that a bulk of the particles which is both unagglomerated and unmixed with a coarse carrier, is sufficiently free flowing to be filled into capsules on an automatic filling machine and to empty from an opened capsule in an inhalation device.
2. An inhalation drug in finely divided and unagglomerated form, wherein a substantial proportion of the individual drug particles have a spherical, collapsed spherical or ring doughnut shape.
3. A drug according to Claim 2 which contains sodium cromoglycate and wherein the particles are of ring doughnut shape.
4. A finely divided inhalation drug, wherein the permeametry: BET ratio is in the range 0.5 to 1.0.
5. A drug according to any one of the preceding claims, wherein the particle density is from 1.3 to 1.7 g cm<sup>3</sup>.
6. A drug according to any one of the preceding claims, having a loose bulk density of greater than 0.3g/cm<sup>3</sup>.
7. A drug according to any one of the preceding claims having a packed bulk density of from 0.4 to 0.75g/cm<sup>3</sup>.
8. A drug comprising sodium cromoglycate, wherein more



than 90% of the drug particles are less than 60 microns in diameter and the drug has a loose bulk density of greater than  $0.3\text{g/cm}^3$ .

5 9. A drug comprising sodium cromoglycate, wherein more than 90% of the drug particles are less than 60 microns in diameter and the drug has a packed bulk density of from  $0.4$  to  $0.75\text{g/cm}^3$ .

10 10. A drug according to any one of the preceding claims which comprises a mixture of sodium cromoglycate and a bronchodilator.

11. A drug according to any one of the preceding claims, wherein at least 50% of the drug particles are less than 60 microns in diameter.

15 12. A drug according to Claim 11, wherein at least 50% of the drug particles are less than 10 microns in diameter.

13. A pharmaceutical formulation, capsule or cartridge comprising a drug according to any one of the preceding claims.

20 14. A process for the production of a finely divided drug according to any one of the preceding claims, which comprises atomising and drying a solution of the drug and collecting some or all of the particles which are below 60 microns in diameter.

25 15. A process according to Claim 14, wherein the atomisation and drying is carried out in a spray drying

apparatus comprising an atomiser, a main chamber and at least one cyclone or bag filter.

16. A finely divided inhalation formulation of sodium cromoglycate comprising a therapeutically effective proportion of individual particles comprising sodium cromoglycate and capable of penetrating deep into the lung, characterised in that a bulk of the particles which is both unagglomerated and unmixed with a coarse carrier, is sufficiently free flowing to be filled into capsules on an automatic filling machine and to empty from an opened capsule in an inhalation device, some of the particles being of ring doughnut shape and the permeametry : BET ratio of the particles being in the range 0.5 to 1.0

What we claim is:-

1. A process for the production of a finely divided inhalation drug comprising a therapeutically effective proportion of individual particles capable of penetrating deep into the lung, wherein a bulk of the particles which is both unagglomerated and unmixed with a coarse carrier, is sufficiently free flowing to be filled into capsules on an automatic filling machine and to empty from an opened capsule in an inhalation device, which process comprises atomising and drying a solution of the drug and collecting some or all of the particles which are below 60 microns in diameter.

2. A process according to Claim 1 wherein a substantial proportion of the individual drug particles have a spherical, collapsed spherical or ring doughnut shape.

3. A process according to Claim 2, wherein the drug contains sodium cromoglycate and the particles are of ring doughnut shape.

4. A process according to any one of the preceding claims, wherein the permeability: BET ratio of the product particles is in the range 0.5 to 1.0.

5. A process according to any one of the preceding claims, wherein the particle density of the product particles is from 1.3 to 1.7 g cm<sup>3</sup>.

6. A process according to any one of the preceding

claims, wherein the product particles have a loose bulk density of greater than  $0.3\text{g/cm}^3$ .

7. A process according to any one of the preceding claims, wherein the product particles have a packed bulk density of from 0.4 to  $0.75\text{g/cm}^3$ .

8. A process according to any one of the preceding claims wherein the drug comprises a mixture of sodium cromoglycate and a bronchodilator.

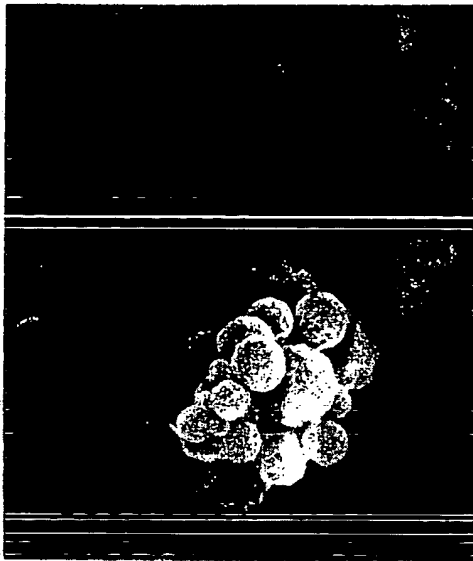
9. A process according to any one of the preceding claims, wherein at least 50% of the drug particles are less than 10 microns in diameter.

10. A process according to any one of the preceding claims, wherein the atomisation and drying is carried out in a spray drying apparatus comprising an atomiser, a main chamber and at least one cyclone or bag filter.

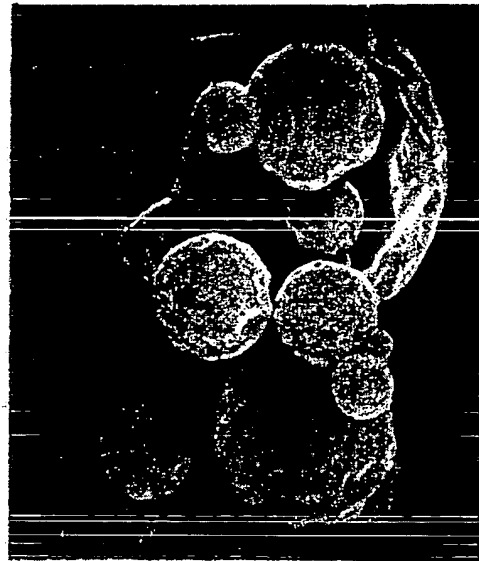
20

25

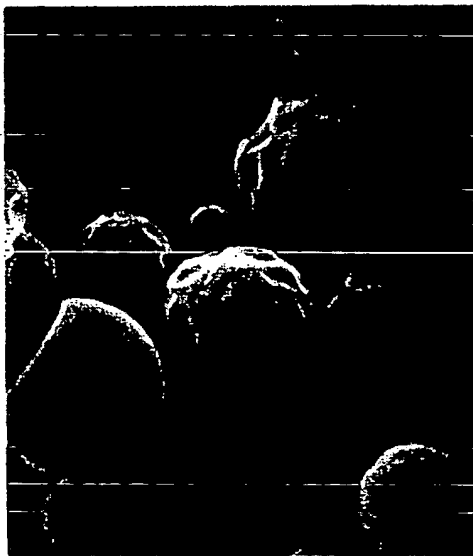
1/12



10 $\mu$ m 2000X



5 $\mu$ m 5000X



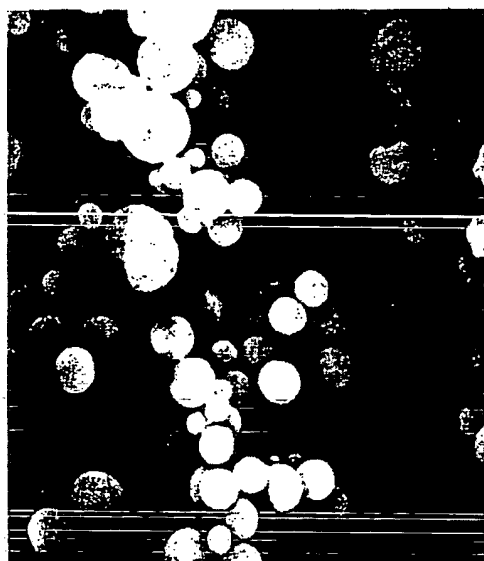
5 $\mu$ m 5000X



2 $\mu$ m 10000X

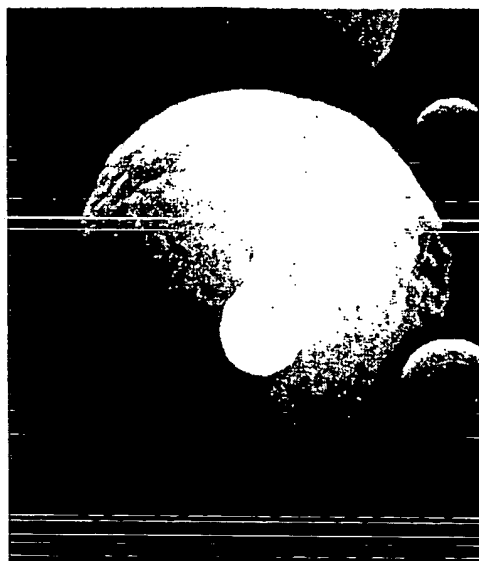
Fig. 1.

2/12



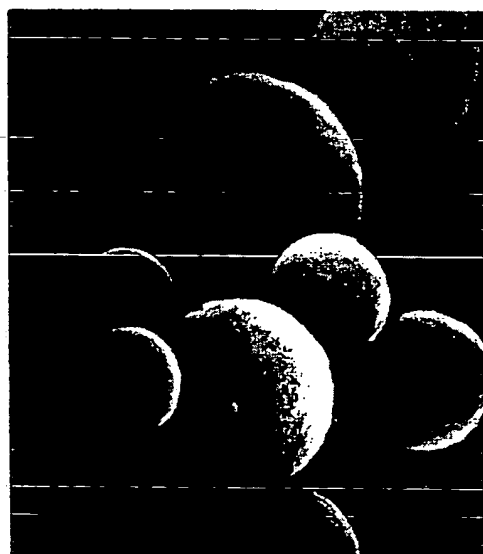
10 $\mu$ m

2000X



5 $\mu$ m

6000X



5 $\mu$ m

5000X



2 $\mu$ m

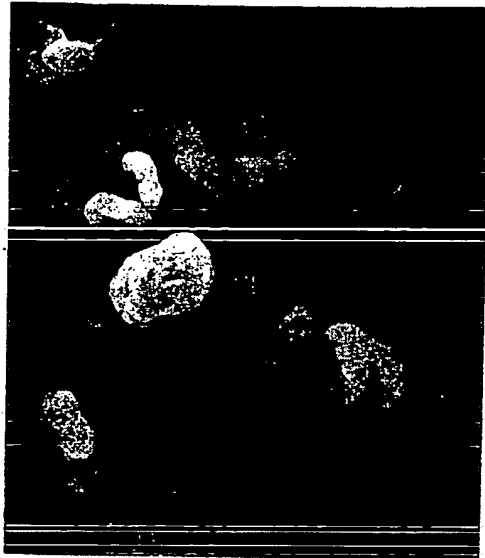
10000X

Fig.2.

UB·U·82

3/12

0072046



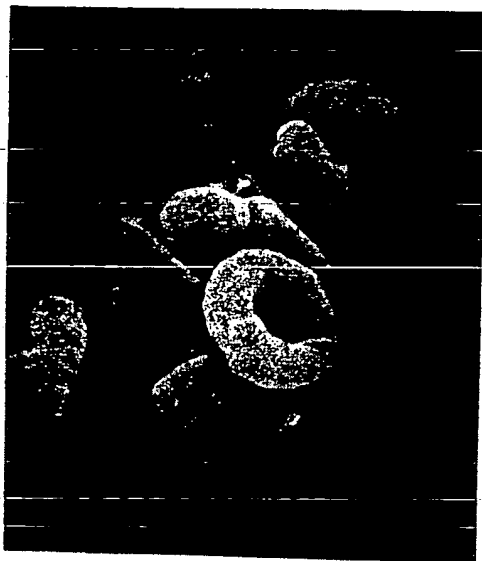
10 $\mu$ m

2000X



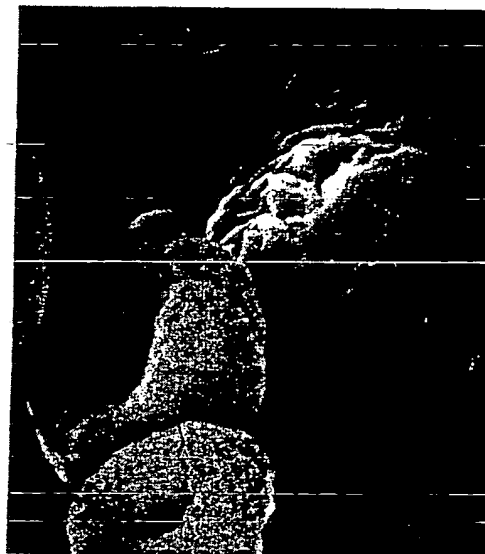
5 $\mu$ m

5000X



5 $\mu$ m

5000X



2 $\mu$ m

10000X

Fig.3.

0072046

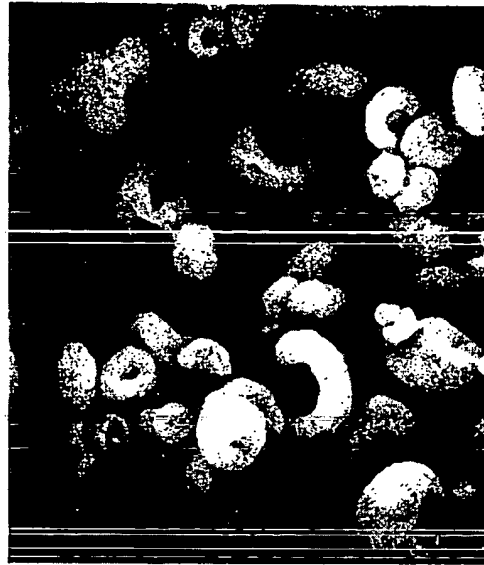
0072046

4/12



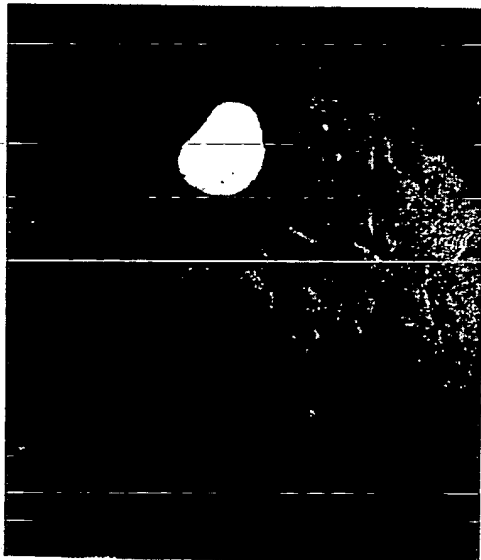
10 $\mu$ m

2000X



10 $\mu$ m

2000X



5 $\mu$ m

5000X



2 $\mu$ m

10000X

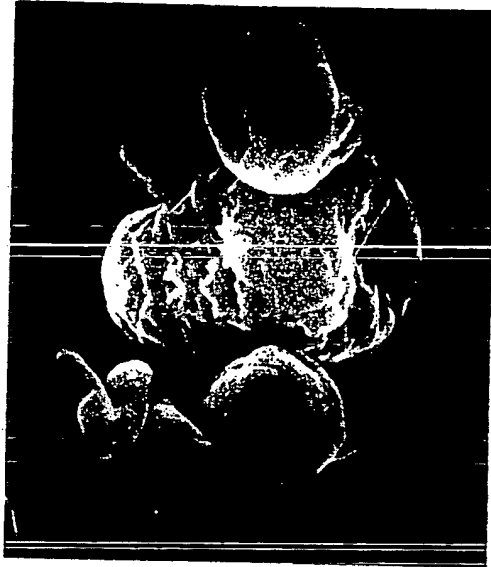
Fig.4.



*Fig. 5.*

6/12

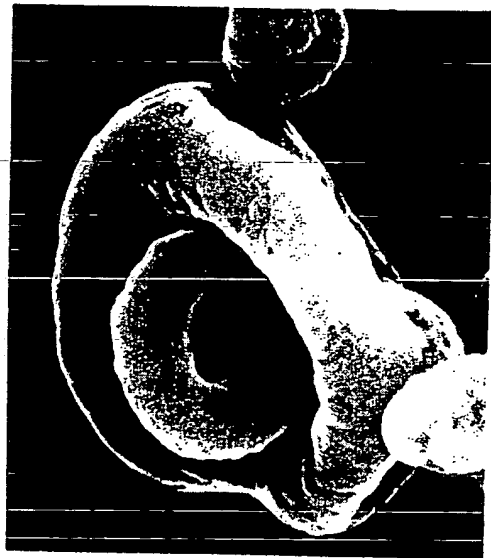
0072046



10 $\mu$ m 2000X



10 $\mu$ m 2000X



5 $\mu$ m 5000X

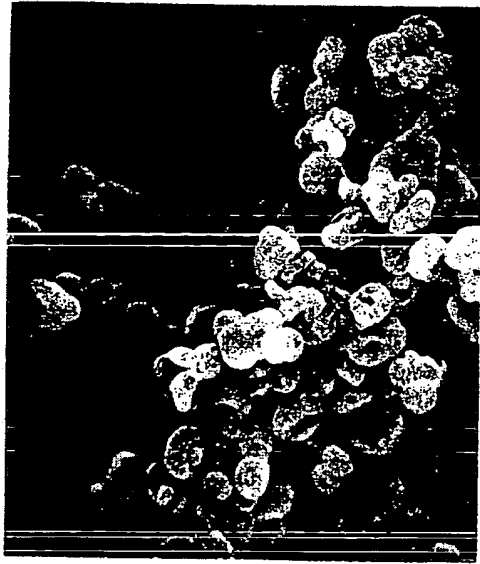


2 $\mu$ m 10,000X

Fig.6.

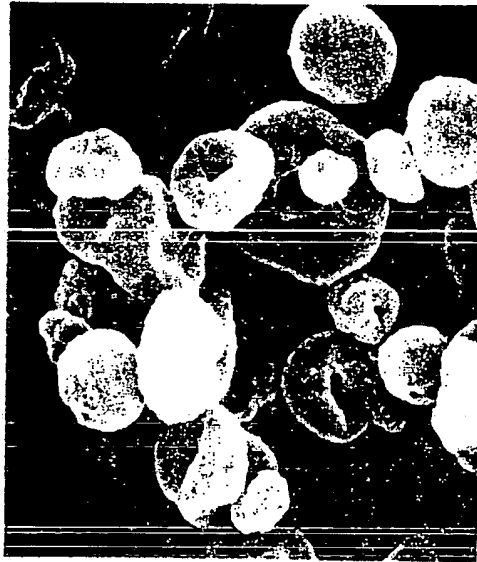
7/12

0072046



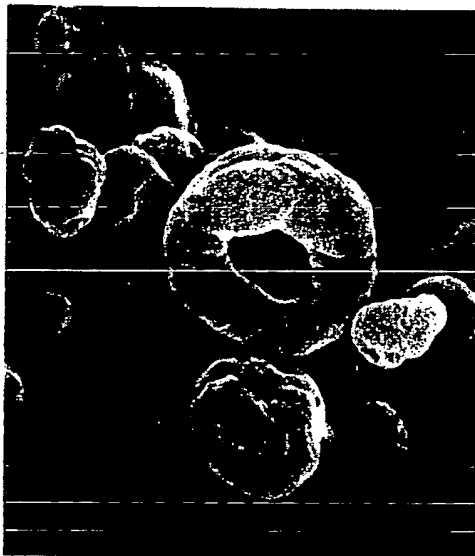
10 μm

2000X



5 μm

5000X



5 μm

5000X

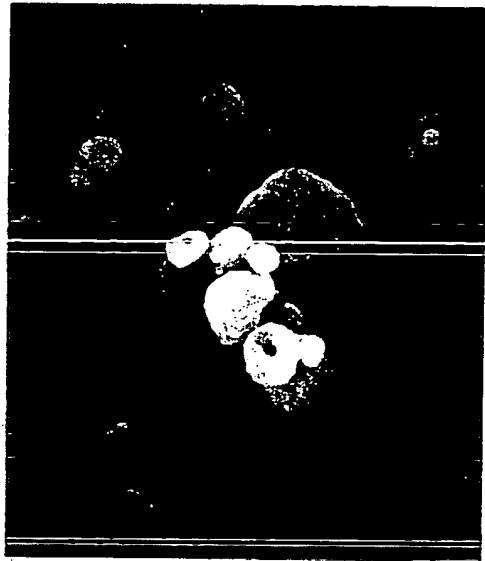


2 μm

10000X

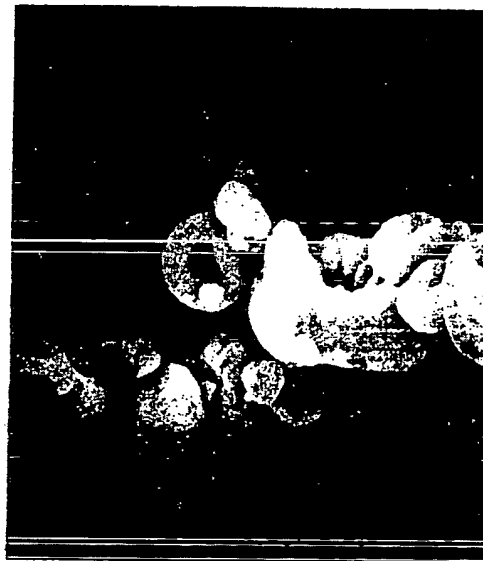
Fig. 7.

8/2



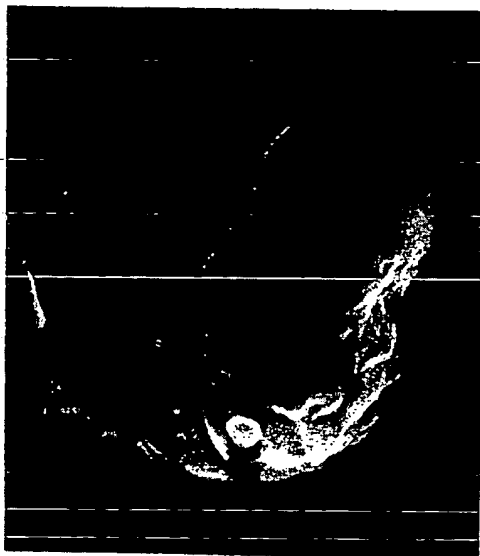
10 $\mu$ m

2000X



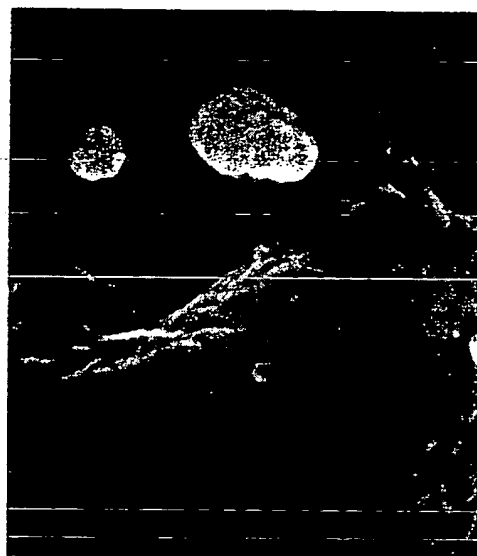
10 $\mu$ m

2000X



5 $\mu$ m

5000X



3 $\mu$ m

10,000X

Fig. 8.

00-01-82

0072046

9/12



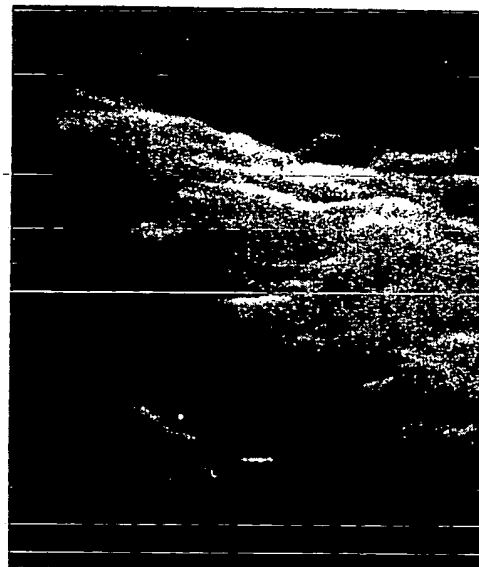
10μm 2000X



10μm 2000X



5μm 5000X

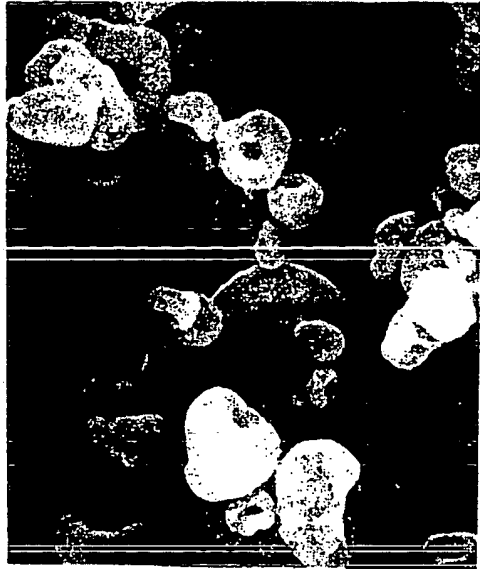


2μm 10,000X

Fig. 9.

10/12

0072046



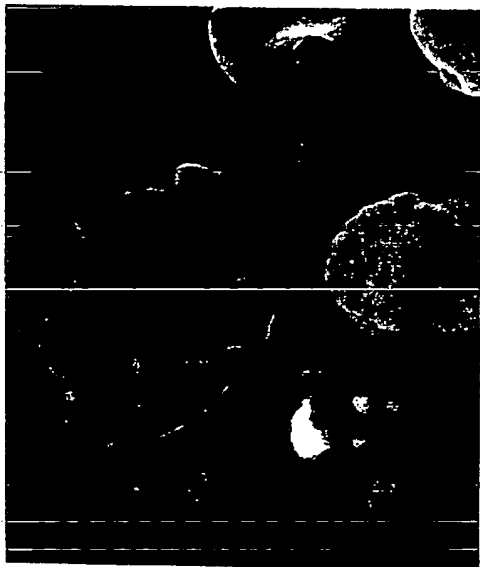
2000X

10μm



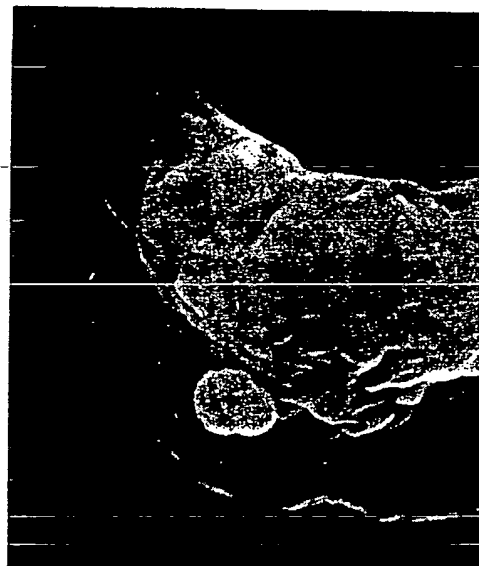
5000X

5μm



5000X

5μm



10,000X

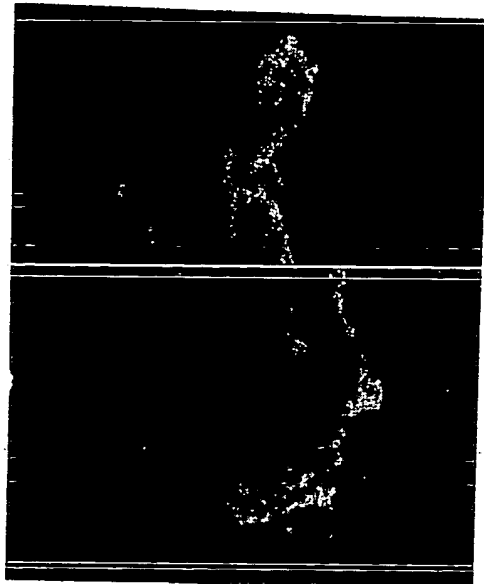
2μm

Fig.10.

0072046

0072046

11/12



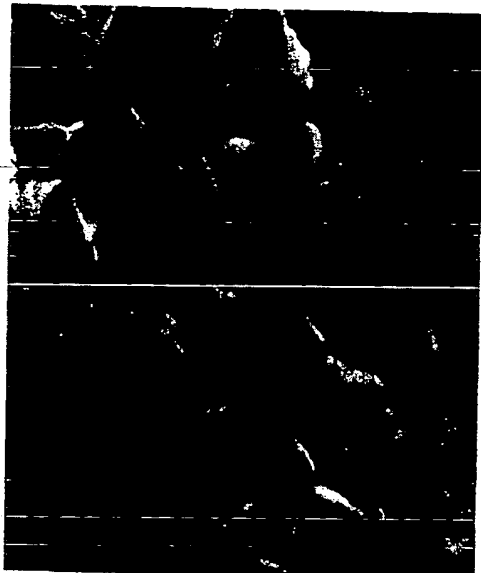
10 $\mu$ m

2000X



10 $\mu$ m

5000X



1 $\mu$ m

10000X



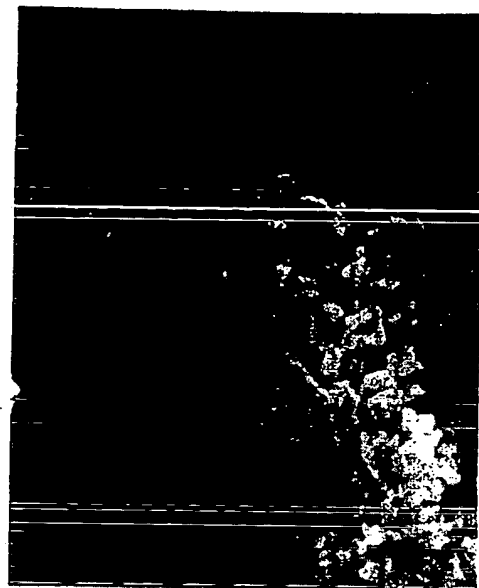
1 $\mu$ m

10000X

Fig.11.

12/12

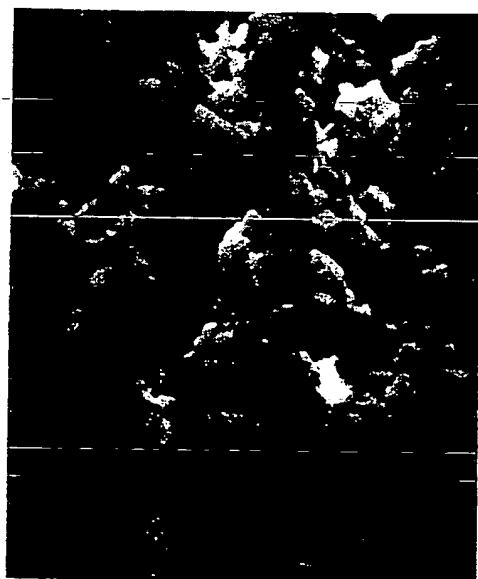
0072046



10  $\mu$ m 2000X



10  $\mu$ m 5000X



10  $\mu$ m 5000X



1  $\mu$ m 10000X

Fig.12.





European Patent  
Office

# EUROPEAN SEARCH REPORT

0072046  
Application number

EP 82 20 0841

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 7)
D,Y	--- US-A-3 957 965 (HARTLEY et al.) * Claim 1; column 2, lines 16-39; column 3, lines 11-14 *	1,14	A 61 K 9/72 A 61 K 31/35
Y	--- GB-A-1 569 611 (FISONS)  * Page 4, lines 28-32, 35; page 5, lines 22-29; claims 19-21,26,27,32,33,38,46,58 *	1,11- 14	
Y	--- GB-A-1 520 248 (FISONS) * Claims; page 4, lines 15-23, 28-29, 82-97; page 5, lines 14-28 *	1,14	
D,Y	--- GB-A-1 549 229 (FISONS) * Claims 1-3 *	1,6,7	
			TECHNICAL FIELDS SEARCHED (Int. Cl. 7)
			A 61 K 9/00 A 61 K 31/00 C 07 D 311/00
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 15-11-1982	Examiner WILLEKENS G.E.J.
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons  & : member of the same patent family, corresponding document	